REMARKS

New claims 11-20 have been introduced. Claims 11-16 depend from originally presented claim 8 and are supported at least by originally presented claims 2-5, 9, and 10. Claim 8 as presented is directed to methods of the invention wherein a green porphyrin selected from BPD-MA and A-EA6 is used as the photosensitizer.

Claims 17-20 depend from originally presented claim 7 and are supported at least by originally presented claims 2, 3, 5, and 9. Claim 7 as presented is directed to methods of the invention wherein a green porphyrin is used as the photosensitizer.

The introduction of these new claims has been made for reasons related to business considerations and to better tailor the claims to encompass currently contemplated embodiments of the invention rather than in acquiescence to any position set forth in the Office Action. No new matter has been introduced, and entry of the amendments is respectfully requested.

Preliminary matters

Applicants thank the Examiner for the indication on page 2, of the Office Action mailed May 7, 2003, which indicates that the previous rejections based upon Vincent et al. and under 35 U.S.C. § 112, second paragraph, have been withdrawn. Applicants understand the reference to Vincent et al. to indicate the withdrawal of the previous rejection of claims 1-10 under 35 U.S.C. § 103(a) as unpatentable over Vincent (USP 5,422,362) and Vincent et al. ("Effects of benzoporphyrin derivative monoacid on balloon injured arteries in a swine model of restenosis," in Lasers in Surgery: Advanced Characterization, Therapeutics, and Systems VI, R. Rox Anderson, M.D., Ed. Proc. SPIE 2671, 72-77 (1996)).

Page 2 of the Action also includes the statement that "the herein claimed method of <u>treating, reducing, and inhibiting</u> restenosis or intimal hyperplasia employing green porphyrin, such as BPD-MA and A-EA6 is considered free of prior art" (underlining in the original). Applicants respectfully point out that this appears to be contradictory to the rejection of original claims 7 and 8 under 35 U.S.C. § 103(a) as later asserted in the same Action. A more detailed discussion traversing this rejection follows below.

Rejection under obviousness-type double patenting

Claims 1-10 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 12-19 of U.S. Patent Application No. 09/716,022, which has now been granted as U.S. Patent 6,609,014 B1 (hereafter the '014 patent). Applicants have carefully reviewed the claims of the instant application, the '014 patent, and the statement of the rejection, and respectfully traverse as follows.

The basis of the rejection appears to be the allegations that despite the multiple differences between the instant claims and those of the '014 patent, "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the specific herein claimed dosage regimen" and that "angioplasty is a common procedure employed to treat restenosis or intimal hyperplasia in artery graft, which is commonly used in coronary bypass graft procedure." Applicants respectfully submit that the statement of the rejection fails to present a *prima facie* case of obviousness. Therefore, no *prima facie* case of obviousness-type double patenting is present.

Given the reliance on the claims of a single reference (the '014 patent) in the instant rejection, two critical criteria must be present for a *prima facie* case of obviousness. There must be 1) a motivation to modify the cited reference to arrive at the claimed invention; and 2) a teaching or suggestion of all claim limitations. These two criteria are part of the well settled body of case law for establishing a case of obviousness as set forth by the Court of Appeals for the Federal Circuit ("Federal Circuit") and its predecessor, the Court of Customs and Patent Appeals (CCPA). Applicants respectfully submit that neither of these criteria have been met in the instant case.

As noted above, the statement of the rejection essentially sets forth the position that because the claims of the '014 patent describe a photosensitizer based method to prevent, treat, inhibit, or reduce intimal hyperplasia in a vein graft, artery graft or vascular graft in a subject, it would have been obvious to modify the method to utilize a particular energy dosage and for use in combination with angioplasty. This is despite *the complete absence of any prior art teaching, suggestion or indication motivating the use of the particular energy dosage recited in the instant claims or a use in combination with angioplasty.* In light of this absence, Applicants respectfully submit that the instant rejection is based upon an impermissible "obvious to try" standard.

The instantly claimed invention is conceptually relatively simple. Photosensitizer mediated photodynamic therapy (PDT) is used in adjunct with angioplasty to prevent, treat, inhibit, or reduce restenosis or intimal hyperplasia. The instant claims recite a particular total energy dose of from about 0.25 to about 25 J/cm^2 as part of the PDT.

The claims of the '014 patent, however, are directed to PDT mediated methods to prevent, treat, inhibit, or reduce intimal hyperplasia in a vein graft, artery graft or vascular graft in a subject. As the statement of the rejection recognizes, there is no disclosure or suggestion of the particular total energy dose or of the use in combination with angioplasty.

Despite the above, the statement of the rejection asserts that

> "[o]ne of ordinary skill in the art would have been motivated to employ the specific herein claimed dosage regimen because optimization of dosing regimen is obvious as being within the skilled artisan. Furthermore, **angioplasty is a common procedure employed to treat restenosis or intimal hyperplasia in artery graft**, which is commonly used in coronary bypass graft procedure." (emphasis added, see pages 3 of the Action)

As evident from the above, however, motivation for the modification of the claims of the '014 patent to arrive at the instant claims arises from assertions that "optimization" and "common" procedures are sufficient to lead to the particular invention as claimed. Stated differently, the motivation is based upon the suppositions that any particular energy dosage used by an ordinary artisan would be *prima facie* obvious and that any procedure used in relation to restenosis or intimal hyperplasia in an artery graft would be obvious for use in combination with angioplasty. The asserted motivation, however, is neither disclosed nor suggested by the cited patent.

The inadequacy of the asserted motivation is particularly troubling with respect to the necessary, but absent, reasons for modifying the claimed methods for treating grafts of the '014 patent to be the methods in relation to angioplasty of the instant application. While the standards for a *prima facie* case of obviousness requires that this gap between the claims of the '014 patent and the instant claims be remedied, *the statement of the rejection provides no basis for* ***why*** an artisan of ordinary skill would modify the claims of the '014 patent for use in adjunct with angioplasty.

In the absence of a reason ***why***, Applicants respectfully submit that the rejection is deficient for failing to provide an adequate motivation to modify the claims of the '014 patent to arrive at the claimed invention. The Federal Circuit has reiterated that there are three possible sources for a motivation to modify the teachings of a reference: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998). As noted above, however, the rejection is not supported by a motivation that originates from any of these sources. The nature of the problem, to prevent, treat, inhibit, or reduce restenosis or intimal hyperplasia, certainly does not lead the ordinary artisan to the use the particular energy dosages or the combination with angioplasty as encompassed by the instant claims. The claims of the patent similarly do not provide motivation for any modification. And finally, there is no evidence to support the notion that the knowledge of the ordinary artisan would motivate the modification of the claims of the patent.

This failure to adequately provide a source of motivation for modifying the claims of the patent is even more egregious in light of more recent decisions by the Federal Circuit, which state that "[a]lthough a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability, in whatever form, must nevertheless be 'clear and particular.'" (*Winner Int'l. Royalty Corp. v. Ching-Rong Wang*, 53 USPQ2d 1580, 1586-87 (Fed. Cir. 2000) quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)). Appellants respectfully submit that no "clear and particular" showing of motivation to combine the claims of the '014 patent and the alleged knowledge to optimize or use in adjunct with angioplasty has been presented in the instant rejection. Similarly, the mere allegation of "obvious to optimize" the total energy dose does not meet this standard of "clear and particular" showing of motivation to use a particular total energy dose.

Appellants further note that the facts of the instant application are analogous to the facts in *In re Fine* (837 F2d. 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). The claims in *Fine* were directed to a system for detecting and measuring nitrogen compounds by use of gas chromatography and a nitric oxide detector. The primary reference (Eads) cited against the claims disclosed a system for monitoring sulfur compounds by use of gas chromatography and a device to calculate the concentration of sulfur compounds based on the amount of sulfur dioxide. This is analogous to the claims of the '014 patent, which relate to the use of PDT on vascular grafts while the instant

invention is directed to the use of PDT in adjunct with angioplasty. The secondary reference in *Fine* disclosed a nitric oxide detector in an attempt to fulfill the requirement for the necessary modification of the primary Eads reference. This is analogous to the assertion (in the instant statement of the rejection) of treating a vascular graft with angioplasty. The Federal Circuit held the assertion that "substitution of one type of detector for another in the system of Eads would have been within the skill of the art" as **insufficient** without support or explanation of the conclusion.

The Federal Circuit's view is directly applicable to the facts of the instant case, where there is no support or explanation of why the ordinary artisan would have selected angioplasty as the procedure for use in adjunct with the methods as claimed in the '014 patent. The claims of the patent do not contemplate or suggest use in combination with angioplasty. There is no evidence that all vascular grafts necessarily require angioplasty, and so no suggestion in the claims of the patent or any other source presented in the statement of the rejection to consider modifying the claims of the patent for use in combination with angioplasty. There is similarly no evidence for the use of the instantly claimed energy dose in combination with PDT treatment of vascular grafts in adjunct with angioplasty. Therefore, no motivation to modify the claims of the '014 patent as alleged has been presented as required by law.

Even if the claims of the '014 patent were viewed, as implied in the statement of the rejection indicating that the methods of the patent encompass their use in combination with a variety of other protocols (e.g. angioplasty), Applicants respectfully submit that this would still be in sufficient to render the claimed invention obvious in light of *In re Baird* (29 USPQ2d 1550 (Fed. Cir. 1994)) and related holdings in *In re Deuel* (34 USPQ2d 1210 (Fed. Cir. 1995)), *In re Bell* (26 USPQ2d 1529, 1532 (Fed. Cir. 1993)) and *In re Jones* (21 USPQ2d 1941 (Fed Cir. 1992)).

The claims of the '014 patent are insufficient because they only provide the concept of a PDT protocol for use in the context of vascular grafts. But even with the assertions in the instant statement of the rejection, this can be, at most, no more than an assertion of a genus of methods to treat vascular grafts. This disclosure of a genus as well as a number of species (treatment of particular types of grafts) within the genus, does not include any species like, or similar to, those encompassed by the instant claims.

The Federal Circuit in *Baird, Deuel,* and *Bell* repeatedly set forth the standard that a broad genus does not render a species within the genus obvious. "No particular one of these DNAs can be

obvious unless there is something in the prior art to lead to the particular DNA and indicate that is should be prepared." *Deuel*, 51 F.3d at 1558-9, 34 USPQ2d at 1215; see also *Baird*, 16 F.3d at 382-3, 29 USPQ2d at 1552, and *Bell*, 991 F.2d at 784, 26 USPQ2d at 1531. Similarly, *Jones* stands for the proposition that a genus of operative embodiments known in the prior art does not render claims to a species obvious in the absence of motivation or suggestion to make the species.

Applied to the facts of the instant case, it would **not be obvious** to modify the claims of the '014 patent for use in adjunct with angioplasty unless there is something in the patented claims to lead the ordinary artisan to the particular modification. Applicants respectfully submit that there is nothing in the claims of the '014 patent that would provide such direction to the ordinary artisan. The mere possibility that vascular grafts *may possibly someday* be treated with angioplasty does not necessarily lead to the instantly claimed invention. This follows because the broad genus of methods encompassed by the claims of the '014 patent simply does not lead to the specific methods of the instant invention. Moreover, the allegation of a motivation in the statement of the rejection fails to remedy this deficiency by providing evidence of the necessary suggestion or motivation. Without this necessary suggestion or motivation as required by *Baird, Deuel, Bell*, and *Jones*, the instant rejection is an impermissible hindsight reconstruction of the claimed invention using the claims of the '014 patent.

Therefore, and in light of the well settled jurisprudence exemplified by *Rouffet*, *Winner, Dembiczak* and *Fine* as well as *Baird, Deuel, Bell*, and *Jones*, the instant rejection is deficient for failing to be adequately supported by motivation to modify the cited reference as required by law. While this error alone is sufficient to require withdrawal of the rejection, Applicants note that the rejection also fails to provide an adequate basis to teach or suggest the important claim limitations relating to the total energy dose as recited in the instant claims. This aspect of the invention as claimed is **not** found in the claims of the '014 patent, and the statement of the rejection fails to provide any basis, beyond mere assertion by the Examiner, for its presence as required for a *prima facie* rejection. In light of this deficiency, the rejection should be withdrawn.

In light of the above, Applicants respectfully submit that the legal requirements for obviousness have not been met and that the instant rejection may be properly withdrawn. Early indication to that effect is urged.

Rejection under 35 U.S.C. § 112

Claims 1-10 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement for use of the term "prevent". Applicants have carefully reviewed the statement of the rejection and traverse for the following reasons.

The statement of the rejection asserts the following (from pages 4-5 of the Action) as supportive of the allegation of non-enablement:

1) the claims encompass "absolute prevention";

2) the absence of a protocol to "prove the efficacy of the presently claimed method in preventing restenosis or IH";

3) there is evidence that "absolute prevention of restenosis or IH is not likely";

4) the quantity of experimentation to "absolutely prevent" restenosis or IH "would be enormously large";

5) it is unpredictable whether "absolute prevention" is possible; and

6) there is no working example of prevention of restenosis or IH in the application as filed.

As evident from the above, the crux of the instant rejection appears to be the assertion that "absolute prevention" is not enabled by the instant application in light of the skill in the art. Applicants respectfully submit, however, that it is the burden of the *prima facie* case to support this position, which would otherwise be a speculative conclusion. Stated differently, it is the Examiner's burden to provide objective reasons why the instantly claimed invention is not enabled with respect to "absolute prevention". This standard is found at MPEP 2164.04, which sets forth the law of *In re Marzocchi* (169 USPQ 367 (CCPA 1971)) where claims must be taken as being enabled unless there is reason to doubt the objective truth of the statements of an application in support of enablement. Applicants respectfully submit that no adequate objective reasons have been provided for why "absolute prevention" in the methods of the invention as claimed, which involve the context of angioplasty, is not enabled. The articles provided in the Information Disclosure Statements (IDS) of record provide no objective information with respect to preventing restenosis or IH in adjunct with angioplasty, which is a particular procedure that is distinct from natural causes of restenosis or IH.

Accordingly, Applicants respectfully submit that no *prima facie* case of non-enablement has been presented.

Moreover, and assuming (solely for the purposes of argument), that there is an issue with respect to whether enablement is present for the practice of "absolute enablement" as asserted by items 1) and 3) above, Applicants respectfully submit that it is well settled law that claims may encompass inoperative embodiments and yet remain patentable. See MPEP 2164.08(b) and the cases cited therein. As set forth therein, "[t]he standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative...." Accordingly, and if the skilled artisan knows that "absolute prevention" is not known in the art (as alleged in the statement of the rejection based upon articles cited in the IDS), there is no deficiency of enablement in the instant claims.

As for item 2) above, Applicants respectfully point out that methods for determining the presence or extent of restenosis or IH in blood vessels are known in the art and no objective reason has been provided as to why they would not be suitable to determine the efficacy of the claimed methods for preventing restenosis or IH in vessels in adjunct with or following angioplasty.

With respect to items 4) and 5) above, Applicants note that the assertions of "enormous" amounts of experimentation and unpredictability are presented as mere conclusions rather than as supported by objective reasons. As noted above, no objective evidence to doubt the ability of the present invention to prevent restenosis or IH, ***in the context of angioplasty***, for extended periods of time, or even in the sense of "absolute prevention" has been presented. Therefore, no objective reasons as to the need for extraordinary experimentation or unacceptable levels of unpredictability have been presented.

Last, and with respect to item 6) above, Applicants respectfully point out that the absence of working examples does not necessarily indicate a lack of enablement. Moreover, and contrary to the assertion, Examples 1 and 2 of the instant application and Figures 1 and 2 do indicate a decrease in intimal thickness upon use of the instantly claimed invention. The statement of the rejection has provided no basis for why a skilled artisan would not find the Examples and the results therefrom supportive of the ability to prevent restenosis or IH as claimed.

In light of the above, Applicants respectfully submit that the claims are enabled for their scope as presented and request withdrawal of the instant rejection.

Prior art rejection under 35 U.S.C. § 103

Claims 1-10 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Vincent (USP 5,422,362) in view of Gonschlor et al. (Photochemistry and Photobiology, 1996: 64(5):758-763) and Harrison (Harrison's Principle of Internal Medicine, 13th ed. 1994, page 986, published by McGraw Hill). Applicants have carefully reviewed the statement of the rejection as well as the cited references and respectfully traverse as follows.

As an initial matter, and as noted above, the rejection appears to be directed to the embodiments of the claims in which porfimer sodium is used as the photosensitizer. Accordingly, the inclusion of claims 7 and 8, directed to the use of green porphyrins and specific members thereof, in the instant rejection appear to be in error.

Moreover, Applicants respectfully point out that the citation of Vincent ('362) appears to be for the descriptions therein of other documents (by Sobeh et al., Dartsch et al., and Eton et al.). While Applicants address the instant rejection as presented, they respectfully request clarification of whether the rejection is based upon the full content of each of these other documents per se, rather than the characterization of them reflected in Vincent ('362).

Turning to the allegations in the statement of the rejection, Applicants again respectfully submit that the passage in column 2, lines 40-57, of Vincent ('362) describes the work of Sobeh et al. as of smooth muscle cells "cultured from the intermedia" of a human long saphenous vein. As the Examiner will no doubt appreciate, the treatment of cells in culture is **not the same as treating restenosis or IH** in a blood vessel that has undergone angioplasty. This is supported by a review of the full disclosures of the two Sobeh et al. documents, which were submitted with the IDS in the instant application. Accordingly, Applicants respectfully submit that the work of Sobeh et al., as reported by Vincent ('362) are **not** pertinent to the instantly claimed invention.

Similarly, the allegations in the statement of the rejection based upon Dartsch et al. also relate to the targeting of cells *in vitro*. This is clearly indicated by a review of Vincent ('362) at column 2, lines 12-39. Therefore, Applicants must again submit that this work by Dartsch et al. is **not** relevant to the instant claims because treating cells *in vitro* is **not the same as treating restenosis or IH** in a blood vessel that has undergone angioplasty.

As for Eton et al. as discussed in Vincent ('362), Applicants' review of the full document (J. Surg. Res. 53:558-562 (1992) provided with Paper No. 8 (IDS of October 10, 2001, mailed

September 25, 2001)) indicates that a more complete understanding of the observations by Eton et al. shows that they provide no support for the instant rejection. As noted by Eton et al. at page 561-562, paragraph bridging the columns,

> "even though the injured segments treated with both photofrin and laser energy developed less intimal hyperplasia than the laser treated segment s which did not receive photofrin, this difference did not reach statistical significance. From this observation, **one could be led to conclude that photofrin added little to the laser treatment**. One possibility, for the reduced degree of intimal hyperplasia seen in the laser only group, is that the amount of laser energy delivered was sufficient to produce some degree of cytotoxicity even in the absence of a photoactivator." (emphasis added)

did not say it is not effective.

In the second full paragraph on page 562, Eton et al. remark that

> "[t]he present study suggests that photodynamic therapy **may be effective** in diminishing the amount of intimal hyperplasia following arterial injury **if administered a week following an endothelial injury.** Further experiments are underway to definitively ascertain the influence of this modality." (emphasis added)

Based on the above, it is rather clear that rather than directing an artisan of ordinary skill toward the use of photofrin and PDT to address intimal hyperplasia (IH) following angioplasty, as encompassed by the claims, Eton et al. raises questions about whether photofrin even contributed to the observed reduction in IH. Instead, Eton et al. clearly indicate that it is not clear whether a photosensitizer was necessary for their effect and that it is a mere possibility that photodynamic therapy "may be effective" against IH, and then only if used "a week following an endothelial injury."

The teachings of Eton et al. thus provide no expectation of success in the practice of the invention as claimed. Instead, and based upon their teachings, *de novo* experimentation is needed, thus rendering the instant rejection based upon an improper "obvious to try" standard.

As noted in *In re O'Farrell* (853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)), an "obvious to try" situation exists "when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if

certain directions were pursued." See *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed Cir. 1990). This describes the instant situation exactly in that the teachings of Eton et al. may pique the curiosity of the ordinary artisan to investigate whether PDT will work against IH in adjunct with angioplasty. But that ordinary artisan has *no expectation that success would result.*

Moreover, the uncertainties evident in the above quoted passages from Eton et al. supports the view, using borrowed language from the Board of Appeals, that Eton et al. is at best but an invitation to scientists to explore a new technology that seems a promising field of experimentation (see *Ex parte Obukowicz*, 27 USPQ2d 1063 (Bd. Pat. App. & Interf. 1993)).

The remaining references in the statement of the rejection do not correct these deficiencies in Eton et al., and thus Vincent ('362). Gonschlor et al. describe the use of photofrin with 100 J of light energy (see page 759, left column) in an experimental porcine model. They further note on page 761, right column, that

> "[t]he use of injury to nondiseased arteries in young pigs is a limitation of the study and we can only therefore conclude the PDT reduced certain aspects of the pathophysiology of restenosis. Thus, perhaps **the results cannot be directly extrapolated to use in human restenosis** where the process occurs in human atherosclerotic vessels...." (emphasis added).

This is followed on page 762, left columns, last paragraph, by "[i]n patients, however, there may be certain limitations in using PDT as described here."

Therefore, and as in the case with Eton et al., Gonschlor et al. provide little more than additional observations to pique the curiosity of the skilled person to experiment further in the general direction in which the instant invention lies. But such experimentation would necessarily be *de novo*, as evidenced by the statements of Gonschlor et al. because the total energy dose, or even a value close thereto, as recited in the instant claims is not disclosed by any reference relied upon in this rejection. The reliance upon the 1.2 J/cm^2 of Dartsch et al. is misplaced because it is for treating cells *in vitro*, which is wholly distinct from the instant claims.

Finally, Harrison provides no disclosure to rectify the deficiencies of Eton et al. or Gonschlor et al. It appears to have been cited solely for the proposition that the use of a stent in combination

with angioplasty is known, as evidenced by the reliance on only a few lines from page 986, which appears to continue on the following page.

In light of the above, and contrary to the assertions in the statement of the rejection, there is no *prima facie* case of obviousness present against the instant claims. The statements on page 8 of the Action set out conclusions of what the ordinary artisan would have been motivated to do without the requisite reason of ***why*** the artisan would have been so motivated. As noted above with respect to obviousness in the traversal of the double patenting rejection, the issue of ***why*** is critical for a *prima facie* case of obviousness. Moreover, a reasonable expectation of success is necessary as discussed above with respect to Eton et al. and Gonschlor et al. Additionally, all the limitations, including the particular total energy dose recited in the instant claims, must be taught or suggested by the cited references.

Because these critical elements to support a case of obviousness are absent, Applicants respectfully submit that no *prima facie* case of obviousness has been presented. Accordingly, this rejection should be withdrawn.

CONCLUSION

In light of the above discussion and traversals, Applicants believe that the claims are in condition for allowance and urge early indication to that effect. The Examiner is encouraged to contact the undersigned to expedite prosecution of the instant application.

In the event that the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **273012012200**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 8, 2003

Respectfully submitted,

By _____

Kawai Lau, Ph.D.
Registration No.: 44,461
MORRISON & FOERSTER LLP
3811 Valley Centre, Suite 500
San Diego, California 92130
(858) 720-5100
Attorneys for Applicant